Correlation of Liver Enzymes and Liver Histology in Chronic Hepatitis B Virus Infection

Kronik Hepatit B Virus Enfeksiyonunda Karaciğer Enzimleri ve Histolojisinin Korelasyonu

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Özet

Amaç: Kronik HBV ile enfeksiyonu olan çocuklarda günümüzde kabul edilen ALT üst sınırının belirgin karaciğer hasarını tespit etmedeki yeterliliğini araştırmak. Gereç ve Yöntem: HBsAg (+) Kronik Hepatit B enfeksiyonu tanısı ile izlenen hastaların, demografik verileri, tanı anındaki HBV DNA ve ALT düzeyleri, karaciğer biyopsi sonuçları retrospektif olarak incelendi. Hastalar ALT düzeylerine göre grup A (ALT<40) ve B (ALT >eşit 40) olmak üzere öncelikle 2 gruba ayrıldı. Grup A daha sonra ALT <25.8 IU/L (A1) ve ALT >eşit 25.8 IU/L (A2) erkekler, ALT<22.1 IU/L (A3) ve ALT>eşit 22.1 IU/l (A4) kızlar olmak üzere 4 alt gruba ayrıldı. Histolojik aktivite indeksi ≥ 4 ve Fibroziz skoru ≥2 belirgin hastalık kriteri olarak alındı. Histopatolojik olarak belirgin hastalık görülmüş olan ALT düzeyleri araştırıldı. Bulgular: Yaş ortalaması 10.09±3.59 yıl olan 34 hepatit B hastası çalışmaya alındı. Grup A da 18, grup B de 16 hasta mevcuttu. Her iki grubun HBV DNA düzeylerinin 3.21±4.41 vs. 1. 77±2.61 109 kopya/ml olduğu görüldü (p= 0.083). Histopatolojik olarak belirgin hastalık Grup A hastalarının %38.9'unda ve grup B hastalarının % 75'inde görüldü (p=0.045). HBV DNA düzeyleri ile HAI ve fibroziz skoru arasında korelasyon tespit edilmedi (sırasıyla r= -0.133, p=0.45 ve r= -0.259, p=0.14). Ortalama HAI ve fibroziz skoru sırasıyla 2.78±2.31 vs. 4.88±2.33 (p=0.013) ve 0.5±0.514 vs. 1.31±1.078 (p=0.007) idi. 9 grup A2 hastasından 5'inde (p=0.045) ve 4 grup A4 hastasından 2'sinde HAI ≥ 4 idi. Tartışma: ALT karaciğer hasarını tespit etmede kullanılabilecek iyi bir belirteçtir. Ancak çocuklarda belirgin karaciğer hasarının tespitinde eşik değerinin 40 IU/L olarak kabul edilmesi uygun değildir.

Anahtar Kelimeler

Alanine Aminotransferaz; Karaciğer; Çocuk; Hepatit

Abstract

Aim: To evaluate the accuracy of current ALT levels in predicting histologically significant liver disease in chronic HBV infected children. Material and Method: Liver biopsies, demographic findings, HBV DNA and ALT levels of HBsAg (+) chronic hepatitis B patients were evaluated retrospectively. Patients were enrolled into group A (ALT<40) or group B (ALT≥40) and further subdivided into males with ALT <25.8 IU/L (A1) and ALT≥25.8 IU/L (A2) and females with ALT <22.1 IU/L (A3) and ALT ≥22.1 IU/L (A4). Significant histology was defined as a fibrosis score ≥ 2 and/or histological activity index (HAI) ≥4. Results: 34 patients with a mean age of 10.09±3.59 were included. There were 18 patients in group A and 16 patients in group B. Mean HBV DNA levels were 3.21±4.41 vs. 1. 77±2.61 109 copies/ml (p= 0.083). 38.9% of group A patients and 75% of group B patients had histological significant disease (p=0.045). There were no correlations between HBV DNA level and HAI and fibrosis score (respectively (r= -0.133, p=0.45) and (r= -0.259, p=0.14)). Mean histological activity index and fibrosis score were 2.78±2.31 vs. 4.88±2.33 (p=0.013) and 0.5±0.514 vs. 1.31±1.078 (p=0.007) respectively in group A and B. Five out of 9 group A2 patients (p=0.045) and 2 out of 4 group A4 patients had HAI ≥ 4. Discussion: ALT level is a good predictor for liver injury. But a cut-off value of 40 IU/L is not the accurate threshold in predicting liver disease probability in children.

Keywords

Alanine Aminotransferase; Liver; Child; Hepatitis

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Introduction

In spite of decline in its incidence, chronic hepatitis B virus (HBV) infection is still a global problem [1,2]. Ninety-five percent of vertically infected neonates, 25-50% of children aged between 1-5 years, and 6-10 % of acutely infected children unfortunately progress to chronic hepatitis B [3,4].

In the natural course of chronic HBV infection, three phases have been recognized: (I) Immune-tolerant phase, (II) Immune-active (Immune-clearance/seroconversion) phase and (III) inactive phase (Postseroconversion) [5]. In the immune-tolerant phase, the immune system does not react against the virus despite the presence of high viral replication. It is characterized by positive HBsAg, HBeAg, high HBV DNA copies, and normal aminotransferases. Most of the perinatal infected children are in this phase and may stay asymptomatic for years. However, some patients progress to the immune-active phase where they have elevated aminotransferases with positive HBsAg, HBeAg, high HBV DNA copies, and negative anti HBs and anti HBe. Since there is a general knowledge that most of the liver injury occurs in the immune-active state, treatment strategies in adult-patient guidelines attempt to shorten the duration of this phase. In these guidelines, the presence or absence of disease activity is assessed by serum ALT (Alanine aminotransferase) and HBV DNA levels. Treatment is offered to those patients with HBV DNA above 2000 IU/ml (>104 copies/ml), elevated ALT levels and any degree of fibrosis, regardless of their HBeAg status [6-8]. Recently the treatment probability of patients with HBV DNA >2000 IU/mL and elevated alanine aminotransferase level, but no evidence of fibrosis, has been emphasized. However, to date none of these reports suggests treatment for patients in the immune-tolerant phase. The rationale of this consensus depends on the fact that patients in the immune-tolerant phase have only minimal hepatic inflammation, limited fibrosis, and poor treatment response. Due to the lack of predicting parameters for associated histological disease in children, these statements are also applied to children.

Traditionally, the upper normal limit of ALT has been 40IU/ml for both men and women. But recently a few studies in adults have pointed out that chronic hepatitis B infected patients with levels of transaminases currently accepted as normal but with high serum hepatitis B virus (HBV) DNA may have significant histological disease [9]. Furthermore, the normal limits of ALT have been revised both for patients and healthy subjects; the upper normal limit of ALT was determined to be far lower than currently accepted limits [10,11]. New recommendations based on these supporting data are 30 IU/L for adult men and 19 IU/L for adult women and 25.8 IU/L in boys and 22.1 IU/L in girls [12-14]. In this context the primary aim of this study is to evaluate the impact of ALT on liver histology and to determine whether there is a significant histological disease even in children with traditionally normal defined ALT levels. Our secondary aim is to evaluate the correlation of liver histology with newly-defined upper normal limits of ALT levels for children.

Patients and Methods: Medical records, demographic findings, pretreatment ALT, and HBV DNA levels of children diagnosed with chronic hepatitis B infection between January 1999 and June 2009 were evaluated retrospectively. Children with at least two serum ALT examinations were included. Alanine aminotransferase levels at biopsy day and HBV DNA levels at liver biopsy week were taken into assessment. Patients were subdivided into two groups according to their serum ALT levels: Group A consisted of children with serum ALT levels <40 IU/L and group B consisted of children with serum ALT levels ≥40 IU/L. Based on the new upper normal limits of ALT in children, group A was further subdivided into four groups as males with ALT levels below and over 25.8 IU/L (A1 and A2 respectively) and females with ALT levels below and over 22.1 IU/L (A3 and A4 respectively). Their pretreatment liver biopsies were re-evaluated by two pathologists who were blinded to ALT and HBV DNA levels. Hematoxylin and eosin stained specimens were scored for necroinflammation and liver fibrosis according to the Knodell scoring system [15]. Trichrome and reticulin stains were used for histopathological assessment of fibrosis. Significant liver histology was defined as fibrosis score ≥2 and/or Knodell histological activity index (HAI) ≥4. Exclusion criteria were obesity (>BMI levels according to age), abnormal lipid profile, co-infection with hepatitis C infection or other viral agents, and liver biopsies performed under or after Hepatitis B treatment. Routine laboratory tests including liver function tests (ALT) were measured with BM Hitachi. HBsAg, HBeAg, Anti HBs, Anti HBe, Anti HBc Ig G and M were analysed with the AxSym system (Abbott) by microparticle enzyme immunoassay. Quantitative HBV DNA analyses were evaluated with the real time polymerase chain reaction (rt PCR) method using the Rotor-Gene 6000 instrument (Corbett Research, Australia) and the Qiagen Artus RG PCR kit (Qiagen, Hamburg, Germany). Liver biopsies were performed percutaneously using 16/18 gauge tru-cut biopsy needles. The study was approved by the local institutional ethic committee and informed consents were obtained from the patients' parents.

Statistical analysis was performed with SPPS for Windows 16.0. Normality distributions of the data were checked with Shapiro-Wilks and Lilliefors test. The chi square test was used to compare the two groups. Before comparing the means, the groups' normality was checked and equality variance was calculated with Levene's test. In case of equal variance the Student-t test was used and the 95% CI interval was calculated. When the variance analysis was not equal and data were not normally distributed, the Mann Whitney U test was used. We performed bivariate correlation analysis and calculated the Spearman coefficient correlation to assess the association between ALT level and histological disease activity. P values of <0.05 were considered statistically significant.

Results: Thirty-four naive (27 boys and 7 girls), HBeAg positive chronic hepatitis B patients aged between 3-18 years (10.9 ±3.5 years) were eligible for the study. All of the patients were vertically infected. Demographic and baseline characteristics of the study group according to serum ALT levels are shown in Table 1. All of the patients except one had HBV DNA level higher than 105 copies/ml. This patient had HBV DNA level of 104 copies/ml and ALT level more than 2 times UNL, which was defined as 40 IU/L in our laboratory.

Nineteen patients had histologically significant disease. Serum ALT levels were positively correlated with HAI (r=0.653, p<0.001) and fibrosis score (r= 0.595, p<0.001). There were no correlations between HBV DNA level and HAI (r= -0.133, p=0-

Table 1. Baseline demographic and histological findings of the patients according to ALT levels.

Patient Characteristics	Group A (ALT<40)			Group B (ALT>40)	Total	p
Number of patients	20-29	30-39	Total			
	10	8	18	16	34	
Gender (M/F)	8/2	13/3	14/4	13/3	27/7	0.8
Age/years	8,3+3,164 (3-13)	10,62+4,24 (3-18)	9,61+2,93 (3-13)	10,62+4,24 (3-18)	10.09+3,59 (3-18)	0.43
ALT IU/L	24.8±2.53	118,88±134,96	29,44±5,95	118,88 ±134,96	71.53±101.710	
HBV DNA (Mean) (log9copies/ml)	3,86±5,46	1,77±2,61	3,21±4,41	1,77±2,61	2,53 ±3,69	0.083
HAI	1,5±2,01	4,88±2,33	2,78±2,31	4,88±2,33	3,76±2,52	0.013
Fibrosis (Mean)	0,3±0,483	1,31±1,078	0,5±0.514	1,31±1,078	0,88±0,91	0.007
Knodell score (Mean)	1,8±2,44	6,19±3,23	3,28±2,761	6,19±3,23	4,65±3,293	0.008

ALT:Alanin Aminotransferase,HAI:Histological Activity Index

.45) and fibrosis score (r= -0.259, p=0.14).

Group A consisted of 18 and group B consisted of 16 children. There were no statistical differences in terms of demographic findings and HBV DNA levels between groups A and B (Table 1). Seven out of 18 (38.9%) group A patients and 12 out of 16 (75.0%) group B patients had histological significant disease (p=0.045).

There were significant differences between two groups in terms of HAI and fibrosis score, with higher scores in group B (Tables 1, 2).

Subgroup analysis was performed in group A. There were 14 males and 4 females. Among males, 5 had ALT levels below 25.8 IU/L (A1) and 9 had ALT levels above 25.8 IU/l (A2). Children in group A2 had significantly higher mean HAI than in A1 (1.0 ±0.0 vs. 1, 56 ±0.52 (%95 CI -1, 08—0,032), p=0.039). None of the patients in group A1 but 5 out of 9 children in group A2 had HAI ≥4 (p= 0.045). None of the male patients in this subgroup had fibrosis in their liver biopsy.

All of the 4 females in the subgroup analysis had ALT levels over 22.1 IU/L (group 4). Two of them had HAI ≥4 and 2 had HAI <4. Their mean HAI was 3.25 ±2.36. Their fibrosis level ranged between 0 and 1 (mean: 0.75 ± 0.5).

Discussion: Although treatment guidelines have not been as clearly defined for children as for adults, reviewers recommend treatment for children over 2 years of age with documented active chronic HBV infection—that is, the presence of HBsAg for 3-6 months, evidence of replication (positive HBeAg and HBV DNA above 20.000 IU/ml or 105 copies/ml), and consistently elevated ALT at least 1.5-2 times the upper normal limit [5,4,16]. To date, several studies have reported some conflicting data about the relationship of viral load and the histological severity of HBV infection. Both adult and child studies demonstrated a positive correlation between HAI, fibrosis, and HBV DNA load [17,18]. In contrast, Shao et al. could not find any relationship between histological grade, stage, and DNA levels in HBeAg positive adults [19]. In the present study, we did not find any correlation between ALT and serum HBV DNA levels, reinforcing the fact that viral load doesn't have any impact on disease severity.

Another marker used to indicate liver injury is ALT. Most of the guidelines take the upper normal limit of ALT as the initial point of treatment indication criterion for antiviral treatment. In Turkey, the criteria currently used for antiviral treatment in children, according to the Ministry of Health reimbursement policy, include a two-fold increase in ALT above the upper normal limit and/or HAI ≥4 and/or fibrosis score ≥2 in a liver biopsy. Liver biopsy is only indicated for those patients with elevated ALT. Despite the high viral load, children with normal ALT levels are assumed to be immune-tolerant and not requiring treatment [9,19].

However, recently concerns have arisen about the absence of histological disease in ALT normal patients. It has become increasingly apparent that previously-defined levels of ALT may underestimate chronic liver disease both in adult and children [9,12,19]. Schwimmer et al. [12] reported new upper normal limits of serum ALT levels as 25.8 IU/L in boys and 22.1 IU/L in girls in the pediatric population.

There is no doubt that high ALT levels have a high prevalence of significant histology [9,19]. In our study, not only the entire group but even the subgroup analysis proved the direct correlation of ALT levels with histological severity. However, 38.8% of patients with normal ALT who were formerly considered to be immune-tolerant and assumed to have mild liver disease also had histologically significant disease. Similarly, in a study evaluating 71 HBV infected children, besides a significant correlation between ALT level and inflammation, 5% of ALT normal patients were found to have HAI≥9 [17]. Also, recent adult studies demonstrated 18-37% significant inflammation and 24-34% significant fibrosis (≥2) even in patients with normal ALT levels [9,20]. Therefore, traditionally defined ALT levels can underestimate chronic liver disease. Based on these emerging data, some authors recommended liver biopsy over age 40 even in normal ALT levels [20]. We also may suggest considering liver biopsy in chronic HBV infected children with currently normal defined ALT levels. However, liver biopsy has some undesirable procedural risks such as bleeding. To avoid over-biopsying we advise using the newly-defined upper limits for liver biopsy decision. There may also be value in some non-invasive tests reflecting liver injury such as transient elastography [21]. But these test needs to be further validated.

Recently, ULN of ALT for children has been reported as 22.1 IU/L for females and 25.8 IU/L for males. None of our patients had histologically significant disease below these thresholds. Although these new cut-off values seem accurate for demonstrating significant histological disease, our study population was very small and insufficient for making an exact recommendation.

Our study is limited by being a single-center, retrospective, small sample size study and by missing genotype analyses. Although it is not exactly defined, there may be an effect of genotype, given that there are controversial results on this issue [18,22]. In conclusion, in contrast to HBV DNA levels, ALT levels seem to be accurate surrogate markers of liver injury. However, a significant proportion of children with currently nor-

Table 2: Histological findings of the patients in both groups.

	Group A (ALT<40) N/%	Group B (ALT≥40) N/%	Total (N/%)	p
HAI				
0	6 (33,3)	2 (12,5)	8 (23,5)	
2	1 (5,6)		1 (2,9)	
3	4 (22,2)	2 (12,5)	6 (17,6)	
4	1 (5,6)	0	1 (2,9)	
5	5 (27,8)	6 (37,5)	11(32,4)	
7	1 (5,6)	6 (37,5)	7 (20,6)	
HAI ≥4	7 (38,8)	12(75)	19 (55,9)	0.034
Fibrosis				
0	9 (50)	3 (18,8)	12 (35,3)	
1	9 (50)	9 (56,2)	18 (52,9)	
2	0	0	0	
3	0	4 (25,0)	4 (11,8)	
4	0	0	0	
Fibrosis ≥2	0	4 (25)	4 (11,8%)	0,024
Knodel score				
0	6 (33,3)	2 (12,5)	8 (23,5)	
1	0	0	0	
2	1 (5,6)	0	1 (2,9)	
3	2 (11,1)	1 (6,2)	3 (8,8)	
4	2 (11,1)	1 (6,2)	3 (8,8)	
5	1 (5,6)	0	1 (2,9)	
6	5 (27,8)	6 (37,5)	11 (32.4)	
7	0	0	0	
8	1 (5,6)	2 (12,5)	3 (8,8)	
9	0	0	0	
10	0	4 (25)	4 (11,8)	
Knodell score ≥4	9 (50)	13 (81,2)	22 (64,7)	0,057
Scheuer grade				
0	6 (33,3)	2 (12,5)	8 (23,5)	
1	2 (11,1)	0	2 (5,9)	
2	10 (55,6)	12 (75)	22 (64,2)	
3		2 (12,5)	2 (5,9)	
Scheuer grade≥2	10 (55,6)	14 (87,5)	24 (70,6)	0,046
Scheuer stage				
0	9 (50)	3 (18,8)	12 (35,3)	
1	5 (27,8)	1 (6,2)	6 (17,6)	
2	4 (22,2)	8 (50)	12 (35,3)	
3	0	4 (25)	4 (11,8)	
Scheuer Stage ≥2	3 (16,7)	11 (68,8)	14 (41,2)	0.002

HAI:Histologcal activity index

mal defined ALT seem to have histologically significant disease. Conventional ALT-dependent treatment indication criteria need to be revised. Also, new cut-off values of ALT that satisfactorily reflect liver damage need to be defined for children.

Competing interests

The authors declare that they have no competing interests.

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